ORGINAL RESEARCH ARTICLE- Pharmacokinetics

Pharmacokinetics and pharmacodynamics of single doses of Rivaroxaban in obese patients before and after bariatric surgery

Running head: Rivaroxaban in bariatric surgery

[1]Dino Kröll*, MD, [1]Guido Stirnimann*, MD; [2]Andreas Vogt, MD, [2]Desirée Lin Lee Lai, MD; [1]Yves Michael Borbély, MD; [1]Julia Altmeier, MD; [3]Sabine Schädelin; [1]Daniel Candinas, MD; [4]Lorenzo Alberio†, MD; [1]Philipp C. Nett†, MD

[1] Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

[2] Department of Anaesthesiology, Inselspital, Bern University Hospital, University of Bern, Switzerland

[3] Department of Clinical Research, Clinical Trial Unit, Spitalstrasse 12, 4031 Basel, Switzerland

[4] Division of Haematology and Central Haematology Laboratory, Centre Hospitalier Universitaire Vaudois, University of Lausanne, CH 1011 Lausanne, Switzerland

Correspondence to:

Dino Kröll, MD (= Principal investigator of the research)

Department of Visceral Surgery and Medicine

University Hospital and University of Bern

CH 3010 Bern

Switzerland

Phone: +41 31 632 21 11, Fax: +416325999

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcp.13243

Lorenzo Alberio, Prof.

Division of Haematology and Central Haematology Laboratory

Centre Hospitalier Universitaire Vaudois, University of Lausanne

CH 1011 Lausanne

Switzerland

Email addresses

dino.kroell@insel.ch*

guido.stirnimann@insel.ch*

yves.borbely@insel.ch

julia.altmeier@insel.ch

andreas.vogt@insel.ch

desiree.lai@bluewin.ch

sabine.schaedelin@usb.ch

daniel.candinas@insel.ch

lorenzo.alberio@chuv.ch†

philipp.nett@insel.ch†

*Shared first authorship

†Equal contributions as senior authors

Keywords

Rivaroxaban; Bariatric surgery; Pharmacokinetics; Pharmacodynamics; Roux-en-Y gastric bypass, Sleeve Gastrectomy; Anticoagulation

Word count: 3494

Number of tables: 3 tables

Number of figures: 4 figures

Author Contributions

Wrote manuscript : D. K., G. S., L. A., S. S.

Designed research : D. K., G. S., L. A., S. S.

Performed research: D. K.; Y. B., J. A., P. N., D. C., A. V., D. L.

Analysed Data: D. K., G. S., L. A., S. S.

Critical review of manuscript: P. N.,Y.B., D. C., A. V., D. L., J.A.

Summary

Aims: Venous thromboembolism is an important cause of postoperative morbidity and mortality in bariatric surgery. Studies of direct oral anticoagulants (DOACs) are not available in this surgical field. The objective of this phase 1 clinical trial was to investigate pharmacokinetic and pharmacodynamic (PK/PD) parameters of rivaroxaban in bariatric patients.

Methods: In this single-centre study, obese patients received single oral doses of rivaroxaban (10 mg) one day before and three days after bariatric surgery. PK and PD parameters were assessed at baseline and during 24 hours after drug ingestion.

Results: Six Roux-en-Y Gastric bypass patients (RYGB) and 6 Sleeve gastrectomy (SG) patients completed the study. Mean rivaroxaban AUC, C_{max}, t_{max} and $T_{1/2}$ were 971.9 µg·h/L (coefficient of variation: 10.6) , 135.3 µg/L (26.7), 1.5 h and 13.1 h (34.1) before and 1165.8 (10.6), 170.0 (26.7), 1.5 and 8.9 (34.1) post-surgery for SG patients and 933.7 µg·h/L (22.3), 136.5 µg/L (10.7), 1.5 h und 13.8 h (46.6) before and 1029.4 (22.3), 110.8 (10.7), 2.5 and 15 (46.6) post-surgery for RYGB patients, respectively. Prothrombin fragments (F1+2) decreased during the first 12 hours and increased thereafter in the pre- and the post-bariatric setting. Thrombin-antithrombin complexes dropped within one to three hours in the pre-bariatric setting and remained low after surgery until they increased at 24 hours post-dose. Rivaroxaban was well tolerated and no relevant safety issues were observed.

Conclusions: Bariatric surgery does not appear to alter PK of rivaroxaban in a clinically relevant way. Effective prophylactic post-bariatric anticoagulation is supported by changes in PD.

WHAT IS KNOWN ABOUT THIS SUBJECT?

Venous thromboembolism represents a significant cause of morbidity and mortality after bariatric surgery.

Thrombosis prophylaxis with rivaroxaban is established in the perioperative setting of orthopaedic patients (hip and knee arthroplasty).

To date, direct oral anticoagulants (DOACs) have not been systematically investigated in bariatric patients.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

This study represents the first systematic PK/PD investigation of prophylactic rivaroxaban doses in bariatric patients.

Single doses of 10 mg rivaroxaban resulted in similar systemic drug exposures before and after bariatric surgery, independent of the bariatric procedure performed.

Effective prophylactic anticoagulation is supported by the pharmacodynamic results of this trial.

TABLES OF LINKS

LIGANDS
Rivaroxaban

TARGETS
S1: Chymotrypsin
Coagulation factor X

These Tables of Links list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (1), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 (2).*

INTRODUCTION

The prevalence of obesity as well as morbid obesity is increasing worldwide and therefore becoming a growing medical and socioeconomic burden (3-5). Bariatric surgery leads to the most sustained reduction of weight and associated co-morbidities, but patients undergoing bariatric surgery are at increased risk of venous thromboembolic events (VTE) (6). Obesity is an independent risk factor for the development of venous thromboembolism itself and the association between obesity and VTE after bariatric surgery is well established (7-9). The incidence of symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) ranges from 0%-5.4% and 0%-6.4%, respectively, but the true incidence remains uncertain (10). Although the overall incidence is low, VTE represents a significant cause of morbidity and mortality after surgery. Even with aggressive prophylaxis, VTE cannot be fully prevented (11-13). The American Society of Metabolic and Bariatric Surgeons (ASMBS) and the American College of Chest Physicians recommend prophylaxis against DVT for all bariatric surgery patients (14). Routine prophylactic perioperative use of low-molecular weight heparins (LMWHs), intermittent pneumatic compression devices and early mobilization are currently the major accepted measures to prevent VTE, particularly in high-risk groups (BMI >50 kg/m^2), advanced age, history of previous VTE, obesity hypoventilation syndrome, open and revisional surgery (13, 15). In clinical practice, physicians lack guidelines supporting their therapeutic decisions regarding LMWH dosing in the field of bariatric surgery. In summary, there exists currently no robust evidence to provide guidance regarding type, dose and duration of antithrombotic prophylaxis after bariatric surgery (15). Due to the fact that most post-discharge VTE events occur within the first 30 days after surgery, extended VTE

prophylaxis should be considered, but the specific duration of chemical prophylaxis is still a matter of discussion (12).

Direct oral anticoagulants (DOACs) are a new class of anticoagulants, whose application is more convenient compared to LMWH. DOACs allow effective and safe anticoagulation and their monitoring is usually not required.

Rivaroxaban is the first oral direct factor Xa inhibitor marketed. It was initially approved for the prevention of venous thromboembolism in patients after elective hip and knee replacement surgery. Rivaroxaban is generally well tolerated and demonstrates a predictable, dose-dependent pharmacology profile up to 24 hours after single dose application. The 10 mg dose of rivaroxaban has a high oral bioavailability (80-100%) irrespective of food intake, a rapid onset of action and the maximum plasma level is achieved two to four hours after oral administration (16, 17). Prophylaxis with rivaroxaban had a significantly higher efficacy in VTE prophylaxis as compared with enoxaparin after hip and knee replacement surgery with similar rates of bleeding (18-21). Friedman et al. compared the efficacy of rivaroxaban in orthopaedic surgery patients with BMI >40 kg/m^2 versus <40 kg/m^2 (posthoc subanalysis of a group of 12,355 patients) and found no difference in the incidence rates of DVT, PE or bleedings (22). Since age, gender or body weight (23) do not seem to alter pharmacokinetics (PK) and phamacodynamics (PD) to a clinically relevant degree, the current recommendation for prophylaxis is 10 mg rivaroxaban once daily in all patients.

However, as pointed out in an editorial by S. Duffull (24), rivaroxaban PK/PD studies indicate a high degree of between-subject variability in the drug concentration-time profile (23). Additionally, the effects of bariatric surgery on PK and PD parameters of DAOCs have not been sufficiently investigated to date, and there is no approved dosing recommendation

for obese patient in the perioperative setting. With this clinical trial, we close part of this knowledge gap and lay ground for a broader investigation of rivaroxaban in morbidly obese patients, especially in the perioperative setting.

METHODS

This single centre open-label, non-randomized phase 1 clinical trial was designed to investigate the single dose PK and PD parameters of rivaroxaban when administered to 12 patients undergoing a planned bariatric surgical procedure (6 Roux-en-Y-Gastric bypass (RYGB) and 6 Sleeve gastrectomy (SG) patients) in the framework of a pilot study.

The trial was approved by the Independent Ethics Committee of Bern, Switzerland, and the Swiss competent authority, Swissmedic. All patients gave written informed consent, and the trial was conducted according to the Declaration of Helsinki, the Good Clinical Practice guideline and local laws and regulations. The study was registered in the ClinicalTrials.gov registry with the identifier number NCT02438098.

Inclusion and exclusion criteria

Eligible patients were men and women, 18 years of age or older, with a BMI $\geq$35 kg/m^2 with planned elective primary laparoscopic bariatric surgery (RYGB or SG). Main exclusion criteria were a history of active bleeding or a high-risk for bleeding, a clinical indication for long-term anticoagulation, and evidence of a thrombosis or PE in the personal history. The decision to perform bariatric surgery was taken independent of this trial.

Study procedure

Enrolled patients received a single oral dose of 10 mg rivaroxaban (Xarelto®, Bayer Pharma AG, Germany) one day prior and three days after surgery under non-fasting conditions. Venous blood samples were taken to assess the pharmacokinetic and pharmacodynamic parameters on both of these days. Blood samples were taken pre-dose (Baseline) and 1, 2, 3, 4, 6, 8, 12 and 24 hours post rivaroxaban administration.

After surgery, use of intermittent pneumatic compression as thrombosis prophylaxis and early mobilization were applied as standard of care. LMWH was started postoperatively 6 hours after closure of the surgical site provided stable haemostasis had been achieved. Patients with BMI <50 kg/m^2 received 40 mg of subcutaneous enoxaparin (Clexane®), those with BMI ≥50 kg/m^2 received 60 mg, respectively. Prophylaxis with LMWH was paused on Study Day 3, when rivaroxaban was investigated.

On the 1st postop day, a gastrographin image series was performed to exclude a postoperative leak. Patients were discharged on day 4 after the surgical intervention. The last study visit occurred at day 30±7, to collect safety data.

Study endpoints

Primary study endpoints were the single dose pharmacokinetic parameters of rivaroxaban after oral administration before and after RYGB and SG. Secondary endpoints were pharmacodynamic parameters as assessed by Thrombin-antithrombin-complexes (TAT), Prothrombin fragments 1 and 2 (F1+2) and D-dimers . Safety endpoints were mortality, clinically evident proximal or distal DVT, PE and all bleeding events.

Sample analysis

Anti Xa activity of heparins and rivaroxaban was measured using the CE labelled chromogenic anti-FXa assay Biophen Heparin 6 (Hyphen BioMed, Neuilly-sur Oise, France). This is a one- stage assay that utilizes endogenous antithrombin. It is an automated kinetic method during which a constant amount of exogenously added bovine FXa is inhibited by anticoagulants in the sample to be tested. Non-inhibited FXa cleaves a FXa-specific chromogenic substrate, producing a yellow signal that is detected at 405 nm. The measured anti-Xa activity was converted to units anti-Xa/ml (LMWH) or ng/ml (rivaroxaban) by the appropriate commercial calibrators, respectively. As for rivaroxaban, the performance of this assay has been evaluated against the standard HPLC-MS method and results were comparable (25).

Prothrombin time (PT) was performed using Innovin (Siemens, Marburg, Germany) as the reagent, the assay was calibrated with a commercial kit containing 4 defined lyophilized plasmas (Siemens), the results are the average of duplicate measurements. Activated partial thromboplastin time (aPTT) is measured with Pathromtin SL (Siemens), the results are the average of duplicate measurements. Coagulation and chromogenic assays were performed on a Behring Coagulation System (BCS) and a CS-5100 automated analyzer (Siemens), respectively (26).

Prothrombin activation fragments 1+2 (F1+2) and thrombin-antithrombin-complexes (TAT) were measured by a quantitative "sandwich" enzyme immunoassay, according to the protocol of the manufactures (Enzygnost® TAT micro and Enzygnost® F1+2 micro, Siemens). The

absorbance was measured using a microtiter plate reader at 492 nm (27). D-dimers concentrations were determined by an automated quantitative immunoassay, according to the manufacturer's instructions (INNOVANCE® D-dimer, Siemens).

Safety and tolerability

Prior to the application of the study drug, every patient received an extensive evaluation including clinical chemistry, haematology and coagulation analyses, an electrocardiogram and clinical workup. After the application of the study medication, safety and tolerability were closely monitored during the first 24 hours by measuring vital signs and specifically asking for untoward symptoms. Adverse events were monitored throughout the study to the final visit at 30 (±7) days post-operation. Each adverse event (AE) was classified according to its severity and seriousness.

Statistics

Demographics and relevant baseline variables are summarized for the per protocol (PP) set in tabular form. Data are stratified by type of surgery (RYGB, SG). Categorical data are presented as frequencies and percentages. For continuous variables, total number of measurements, mean and standard deviation are presented. Per protocol, only descriptive statistical analyses were foreseen.

Pharmacokinetic and pharmacodynamics analysis

Pharmacokinetic parameters were assessed before and after surgery by measuring rivaroxaban concentrations at nine different time points: before administration of study medication and 1, 2, 3, 4, 6, 8, 12 and 24 h thereafter. Non-compartmental PK parameters have been calculated using the R package DescTools (DescTools: Tools for descriptive

statistics. A. Signorelli et al. 2015. R package version 0.99.18, http:// CRAN.R-project.org/package=DescTools). For the calculation of the AUC, a spline-interpolation was used.

For both surgical procedures, the following pharmacokinetic endpoints are presented: AUC: area under plasma concentration curve; C_{max}: peak plasma concentration; $t_{1/2}$: terminal half-life; $V_{z/f}$:= (Dose/C_0)/bodyweight: apparent volume of distribution during the terminal phase divided by total body weight (in kg); t_{max}: time to peak plasma concentration. For some patients t_{max} could not be determined, since its values were the same for two points of time. These measurements were not included in the analysis of t_{max}. C_{max} and t_{max} are presented in tabular and graphical form.

For D-Dimers (DD), Prothrombin fragments (F1+2) and Thrombin-Antithrombin-Complexes (TAT), maximal concentration C_{max} and time to maximal concentration t_{max} is presented in tabular form. Two patients (ID 7 before surgery and ID 12 after surgery) are only partially included in the analysis since no valid PD results were obtained due to technically difficult blood sampling. For the assessment of the pharmacodynamic parameters, measurements at the following points of time were used: 0, 1, 3, 12 and 24 h after the application of the study medication. PK/PD data were only generated and analysed if the patient in fact received the study treatment.

RESULTS

Study population

Between July 19, 2015 and November 25, 2015, thirteen patients were enrolled into the study; one patient was withdrawn before the second application of rivaroxaban for safety reasons. Of the remaining 12 patients, 6 patients had SG and 6 patients were treated with RYGB surgery. Mean age was 39 years for both groups, and the proportion of male patients was 50 and 33% in the SG and in the RYGB group, respectively. Mean BMI was higher in the SG group (44.6 kg/m^2) than in the RYGB group (38.5 kg/m^2). All patients were of Caucasian origin (table 1).

Pharmacokinetics

Single application of 10 mg rivaroxaban resulted in a rivaroxaban area under the curve (AUC) of of 933.7 μg·h/L (prebariatric assessment) and 1029.4 μg·h/L (postbariatric) in the RYGB group and of 971.9 μg·h/L (prebariatric) and 1165.8 (postbariatric) in the SG group, respectively. C_{max} before bariatric surgery was similar in both groups (136.5 in patients RYGB versus 135.3 μg/L in SG patients), whereas after the bariatric intervention C_{max} was lower in RYGB patients (110.8 μg/L) and higher in patients after SG (170 μg/L). Mean t_{max} was slightly delayed after bariatric intervention in the RYGB group (1.5 versus 2.5 h) but not in the SG group (1.5 h). However, the range was similar for both groups and both assessments (pre- and postbariatric). Half-life of rivaroxaban was similar in both groups before and after bariatric surgery (table 1). PK curves of the two different surgical procedures are displayed in figure 1. Pharmacodynamic parameters are summarized in table 2.

Pharmacodynamics

Pharmacodynamic effects of rivaroxaban has been evaluated by the assessment of Thrombin-antithrombin-complexes (TAT), Prothrombin fragments F1+2 and D-dimers.

Thrombin-antithrombin-complexes decreased in the preoperative setting within the first one to three hours after the application of rivaroxaban. Values significantly dropped within one hour from a median TAT concentration of 10.6 to 2.6 and from 13.7 to 2.8 ng/ml for the RYGB and the SG group, respectively, and this effect was maintained for at least 12 hours after the application of rivaroxaban. After 24 hours, TAT values increased slightly but were still lower than those values prior to the application of rivaroxaban for both groups in the preoperative setting (figure 2, figure S1, table S1).

Postoperatively, TAT values were already decreased before the application of rivaroxaban, due to the fact that patients received prophylactic low molecular weight heparin the day before as part of standard of care. However, a further slight decrease in these values was observed both three and twelve hours after the application of rivaroxaban on Study Day 3. After 24 h, TAT values increased similar to the increase observed in the assessment taken prior to the surgical intervention (figure 2, figure S1, table S1).

Similar to TAT, F1+2 are characterized by a relevant drop after the application of rivaroxaban. Decrease of concentration is most prominent 12 h after the application of rivaroxaban (reduction of median F1+2 concentration within 12 hours from 269 to 119 and from 212 to 71 pmol/L for the RYGB and the SG group, respectively) whereas values rise towards the initial level after 24h (figure 3, figure S2, table S1). The dynamic changes observed with F1+2 was similar in the pre- and postoperative setting.

D-dimers decrease slightly during the first 12 hours after the application of rivaroxaban (reduction of median D-dimers concentrations from 708 to 657 and from 629 to 572 ng/ml over 12 hours for the RYGB and the SG group, respectively) and increase to the initial D-dimer level 24 h after the application of rivaroxaban. In the postoperative setting, D-dimer values are generally higher than in the preoperative assessment but the dynamic changes observed are comparable to the preoperative setting (figure 4, figure S3, table S1).

The pharmacodynamic parameters of two patients with SG (one patients in the presurgical and one in the postsurgical group) were excluded from further analysis due to false positive values that have been attributed to technical problems during the collection of the blood sample.

Safety and tolerability

All recorded adverse events and serious adverse events are listed in table 3 together with the safety measures taken. There was only one serious adverse event. This patient suffered from a jejunal obstruction after RYGB that was unrelated to the study intervention but required surgical revision. This patient was withdrawn from the study and from the per protocol analysis set. Only in two events, the relationship to the study medication was rated as "possible" and both events were assessed as mild and moderate in intensity (table 3).

DISCUSSION

Single doses of 10 mg rivaroxaban resulted in similar systemic exposures, as measured by AUC, both before and after bariatric surgery, regardless of the type of bariatric procedure performed. In contrast to what might have been expected, the AUC values of both surgical

groups were higher in the postoperative setting, compared to the preoperative setting. Maximum concentrations (C_{max}) were higher in the SG group postoperatively and lower in the RYGB group compared to the pre-surgical assessment. However, this effect is less pronounced than what has been observed with different 10 mg galenic formulations of rivaroxaban and lies in the expected range of variation of other non-obese patient groups (17, 28). In the postoperative setting of RYGB patients t_{max} is slightly delayed, but the range remains unaffected. Overall, AUC of 10 mg rivaroxaban in this obese study population (before surgery 952.6 µg·h/L, after surgery 1095.5 µg·h/L) was similar to the AUC in healthy individuals with normal BMI (1020/14.9 µg·h/L) and patients after total hip replacement surgery (1170 µg·h/L) that have been exposed to the same dose and formulation of rivaroxaban supporting the finding that the AUC is not affected in a significant way by bariatric surgery (17, 29).

Prophylactic doses of rivaroxaban administered prior to the bariatric surgery led to a rapid pharmacodynamic response with a significant (>70%) median decrease of TAT within one hour after the exposition to the anticoagulant. In the postoperative groups the initial drop of TAT was less pronounced since the patients already received LMWH the day prior to the application of rivaroxaban as part of the standard prophylactic treatment. TAT levels 24 hours after the exposition to rivaroxaban did not return to normal as compared to preoperative levels prior to the ingestion of rivaroxaban but to a range observed one to three hours after the application of rivaroxaban.

Additionally, the pharmacodynamic effects as measured by prothrombin activation fragments is characterized by a significant (>55%) median drop of F1+2 value within the timeframe of

12 hours. After 24 h, prothrombin activation fragments remained below the levels measured prior to the administration of rivaroxaban in the preoperative groups, whereas in the postoperative group F1+2 levels were equal to the levels measured before the administration of rivaroxaban, most likely reflecting the effect of previously administered LMWH.

The delayed response of F1+2 compared to TAT is explained by its longer half-life (about 90 min) compared to TAT (about 10 min) (30). For D-dimers, that are characterized by an even longer half-life (around 8-12 h), only a slight decrease of concentration could be observed 12 hours after rivaroxaban ingestion.

With the exception of baseline levels of F1+2 and particularly TAT, pharmacodynamic values in the postsurgical analyses were higher compared to the presurgical investigations as consequence of the procoagulant effect of the surgical intervention. This observation may indicate that the same dose of anticoagulant is slightly less effective in controlling the postoperatively increased procoagulant state.

Kubitza et al. investigated pharmacokinetics , pharmacodynamics and the safety profile of 10 mg single dose rivaroxaban administration in different body weight groups. Interestingly, AUC values were stable across all weight groups: 1172 µ·h/L in female patients ≤50 kg, 1029 µ·h/L in patients weighing 70-80 kg, and 1155 µ·h/L in the >120 kg but <150 kg weight group. The results of our study indicate, too, that neither increased body weight nor the bariatric intervention significantly affect the pharmacokinetic and pharmacodynamics parameters of the drug (pre bariatric AUC 952.6 µ·h/L, post bariatric AUC 1095.5 µ·h/L). The most probable explanation to this observation is the low volume of distribution of rivaroxaban. In fact, rivaroxaban is extensively bound to plasma proteins und has a relatively

low tissue affinity (31). In the trial of Kubitza et al. women in the ≤50 kg weight group showed an increased C_{max} (178 µg/L) whereas rivaroxaban AUCs were similar in all groups. Our results demonstrate a higher C_{max} (170 µg/L) and an increased inter-individual variability of postoperative rivaroxaban plasma levels in the SG group but a slightly decreased C_{max} (110 µ/L) and an increased t_{max} (plus 1 h, range unaffected) in the RYGB group, again with similar AUCs in both surgical groups before and after the bariatric intervention. Reasons for these observations may be an increased variability in gastric passage time in patients who had bariatric surgery directly affecting the stomach, and alterations in the site of drug absorption in RYGB patients as a consequence of the partially bypassed stomach and the bypassed duodenum. However, these observations are within the known variations of rivaroxaban pharmacokinetic parameters.

Overall, prophylactic application of rivaroxaban in bariatric patients resulted in pharmacokinetic results comparable to those reported from prior trials and the assessment of pharmacodynamic parameters supports the clinical effectiveness of a 10 mg rivaroxaban dose in obese patients.

The data obtained from our trial supports these original results and also expands our understanding of the clinical pharmacology of rivaroxaban, specifically showing that the pharmacokinetic and pharmacodynamic properties remain unaltered after SG and RYGB. This clinical trial is the first systematic investigation of rivaroxaban in bariatric surgery patients. It shows that there were no relevant alterations in the clinical pharmacology profile of rivaroxaban in the postoperative setting compared to results obtained prior to the surgical intervention. Single doses of 10 mg rivaroxaban showed an unremarkable safety profile

without clinically relevant signs of bleeding after bariatric surgery and there was no thrombotic event observed during this clinical trial.

Limitations of this phase 1 clinical trial are the relatively small sample size and the single applications of rivaroxaban. However, it is important to note that rivaroxaban does not have significant accumulation after multiple doses, so that the single-dose profile is predictive of the multiple dose profile in patients without impaired renal function.

Another limitation is the short interval between the surgical intervention and the application of rivaroxaban. Although this takes into account the timeframe at interest for a prophylactic postoperative anticoagulation, it is not known whether pharmacokinetic parameters remain unchanged over the following period of weight loss and post-surgical functional adaptations of the GI-tract.

In conclusion, single doses of 10 mg rivaroxaban had a favourable pharmacokinetic, pharmacodynamic, and safety profile in this limited bariatric surgery collective. The results of this study will help to design larger trials with clinical endpoints in this particular patient population with the final goal of safe and efficacious use of rivaroxaban in morbidly obese patients.

Acknowledgements

The authors would like to thank Kenneth Todd Moore for review and proofreading of the manuscript and Christiane Gerschheimer (Central Haematology Laboratory, CHUV, Lausanne, Switzerland) for her skilled laboratory support

CONFLICT OF INTEREST STATEMENT

Dino Kröll, Guido Stirnimann, Andreas Vogt, Desirée Lin Lee Lai, Yves Michael Borbély, Julia Altmeier, Sabine Schädelin, Daniel Candinas, Philipp Christoph Nett declare that they have no conflict of interest.

Lorenzo Alberio has received travel grants and consultancy fees from Bayer; he is member of the Swiss Advisory Board for the clinical use of Rivaroxaban in VTE and of the working group RIVAMOS (25).

There are no commercial interests related to the subject of this manuscript.

Financial or material support: This clinical trial has been supported by a grant of Bayer (Schweiz) AG, Medical Department, Grubenstrasse 6, CH 8045 Zürich, Switzerland

REFERENCES

1. Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, Buneman OP, Davenport AP, McGrath JC, Peters JA, Spedding M, Catterall WA, Fabbro D, Davies JA, Nc I. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucleic Acids Res. 2016;44(D1):D1054-68.
2. Alexander SP, Davenport AP, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Southan C, Davies JA, Collaborators C. The Concise Guide to PHARMACOLOGY 2015/16: G protein-coupled receptors. Br J Pharmacol. 2015;172(24):5744-869.
3. Collaborators GBDRF, Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, Biryukov S, Brauer M, Burnett R, Casey D, Coates MM, Cohen A, Delwiche K, Estep K, Frostad JJ, Astha KC, Kyu HH, Moradi-Lakeh M, Ng M, Slepak EL, Thomas BA, Wagner J, Aasvang GM, Abbafati C, Abbasoglu Ozgoren A, Abd-Allah F, Abera SF, Aboyans V, Abraham B, Abraham JP, Abubakar I, Abu-Rmeileh NM, Aburto TC, Achoki T, Adelekan A, Adofo K, Adou AK, Adsuar JC, Afshin A, Agardh EE, Al Khabouri MJ, Al Lami FH, Alam SS, Alasfoor D, Albittar MI, Alegretti MA, Aleman AV, Alemu ZA, Alfonso-Cristancho R, Alhabib S, Ali R, Ali MK, Alla F, Allebeck P, Allen PJ, Alsharif U, Alvarez E, Alvis-Guzman N, Amankwaa AA, Amare AT, Ameh EA, Ameli O, Amini H, Ammar W, Anderson BO, Antonio CA, Anwari P, Argeseanu Cunningham S, Arnlov J, Arsenijevic VS, Artaman A, Asghar RJ, Assadi R, Atkins LS, Atkinson C, Avila MA, Awuah B, Badawi A, Bahit MC, Bakfalouni T, Balakrishnan K, Balalla S, Balu RK, Banerjee A, Barber RM, Barker-Collo SL, Barquera S, Barregard L, Barrero LH, Barrientos-Gutierrez T, Basto-Abreu AC, Basu A, Basu S, Basulaiman MO, Batis Ruvalcaba C, Beardsley J, Bedi N, Bekele T,

Bell ML, Benjet C, Bennett DA, Benzian H, Bernabe E, Beyene TJ, Bhala N, Bhalla A, Bhutta ZA, Bikbov B, Bin Abdulhak AA, Blore JD, Blyth FM, Bohensky MA, Bora Basara B, Borges G, Bornstein NM, Bose D, Boufous S, Bourne RR, Brainin M, Brazinova A, Breitborde NJ, Brenner H, Briggs AD, Broday DM, Brooks PM, Bruce NG, Brugha TS, Brunekreef B, Buchbinder R, Bui LN, Bukhman G, Bulloch AG, Burch M, Burney PG, Campos-Nonato IR, Campuzano JC, Cantoral AJ, Caravanos J, Cardenas R, Cardis E, Carpenter DO, Caso V, Castaneda-Orjuela CA, Castro RE, Catala-Lopez F, Cavalleri F, Cavlin A, Chadha VK, Chang JC, Charlson FJ, Chen H, Chen W, Chen Z, Chiang PP, Chimed-Ochir O, Chowdhury R, Christophi CA, Chuang TW, Chugh SS, Cirillo M, Classen TK, Colistro V, Colomar M, Colquhoun SM, Contreras AG, Cooper C, Cooperrider K, Cooper LT, Coresh J, Courville KJ, Criqui MH, Cuevas-Nasu L, Damsere-Derry J, Danawi H, Dandona L, Dandona R, Dargan PI, Davis A, Davitoiu DV, Dayama A, de Castro EF, De la Cruz-Gongora V, De Leo D, de Lima G, Degenhardt L, del Pozo-Cruz B, Dellavalle RP, Deribe K, Derrett S, Des Jarlais DC, Dessalegn M, deVeber GA, Devries KM, Dharmaratne SD, Dherani MK, Dicker D, Ding EL, Dokova K, Dorsey ER, Driscoll TR, Duan L, Durrani AM, Ebel BE, Ellenbogen RG, Elshrek YM, Endres M, Ermakov SP, Erskine HE, Eshrati B, Esteghamati A, Fahimi S, Faraon EJ, Farzadfar F, Fay DF, Feigin VL, Feigl AB, Fereshtehnejad SM, Ferrari AJ, Ferri CP, Flaxman AD, Fleming TD, Foigt N, Foreman KJ, Paleo UF, Franklin RC, Gabbe B, Gaffikin L, Gakidou E, Gamkrelidze A, Gankpe FG, Gansevoort RT, Garcia-Guerra FA, Gasana E, Geleijnse JM, Gessner BD, Gething P, Gibney KB, Gillum RF, Ginawi IA, Giroud M, Giussani G, Goenka S, Goginashvili K, Gomez Dantes H, Gona P, Gonzalez de Cosio T, Gonzalez-Castell D, Gotay CC, Goto A, Gouda HN, Guerrant RL, Gugnani HC, Guillemin F, Gunnell D, Gupta R, Gupta R, Gutierrez RA, Hafezi-Nejad N, Hagan H, Hagstromer M, Halasa YA, Hamadeh RR, Hammami M, Hankey GJ, Hao Y, Harb HL, Haregu TN, Haro JM, Havmoeller R, Hay SI, Hedayati MT, Heredia-Pi IB, Hernandez L, Heuton KR, Heydarpour P, Hijar M, Hoek HW, Hoffman HJ, Hornberger JC, Hosgood HD, Hoy DG, Hsairi M, Hu G, Hu H, Huang C, Huang JJ, Hubbell BJ, Huiart L, Husseini A, Iannarone ML, Iburg KM, Idrisov BT, Ikeda N, Innos K, Inoue M, Islami F, Ismayilova S, Jacobsen KH, Jansen HA, Jarvis DL, Jassal SK, Jauregui A, Jayaraman S, Jeemon P, Jensen PN, Jha V, Jiang F, Jiang G, Jiang Y, Jonas JB, Juel K, Kan H, Kany Roseline SS, Karam NE, Karch A, Karema CK, Karthikeyan G, Kaul A, Kawakami N, Kazi DS, Kemp AH, Kengne AP, Keren A, Khader YS, Khalifa SE, Khan EA, Khang YH, Khatibzadeh S, Khonelidze I, Kieling C, Kim D, Kim S, Kim Y, Kimokoti RW, Kinfu Y, Kinge JM, Kissela BM, Kivipelto M, Knibbs LD, Knudsen AK, Kokubo Y, Kose MR, Kosen S, Kraemer A, Kravchenko M, Krishnaswami S, Kromhout H, Ku T, Kuate Defo B, Kucuk Bicer B, Kuipers EJ, Kulkarni C, Kulkarni VS, Kumar GA, Kwan GF, Lai T, Lakshmana Balaji A, Lalloo R, Lallukka T, Lam H, Lan Q, Lansingh VC, Larson HJ, Larsson A, Laryea DO, Lavados PM, Lawrynowicz AE, Leasher JL, Lee JT, Leigh J, Leung R, Levi M, Li Y, Li Y, Liang J, Liang X, Lim SS, Lindsay MP, Lipshultz SE, Liu S, Liu Y, Lloyd BK, Logroscino G, London SJ, Lopez N, Lortet-Tieulent J, Lotufo PA, Lozano R, Lunevicius R, Ma J, Ma S, Machado VM, MacIntyre MF, Magis-Rodriguez C, Mahdi AA, Majdan M, Malekzadeh R, Mangalam S, Mapoma CC, Marape M, Marcenes W, Margolis DJ, Margono C, Marks GB, Martin RV, Marzan MB, Mashal MT, Masiye F, Mason-Jones AJ, Matsushita K, Matzopoulos R, Mayosi BM, Mazorodze TT, McKay AC, McKee M, McLain A, Meaney PA, Medina C, Mehndiratta MM, Mejia-Rodriguez F, Mekonnen W, Melaku YA, Meltzer M, Memish ZA, Mendoza W, Mensah GA, Meretoja A, Mhimbira FA, Micha R, Miller TR, Mills EJ, Misganaw A, Mishra S, Mohamed Ibrahim N, Mohammad KA, Mokdad AH, Mola GL, Monasta L, Montanez Hernandez JC, Montico M, Moore AR, Morawska L, Mori R, Moschandreas J, Moturi WN, Mozaffarian D, Mueller UO, Mukaigawara M, Mullany EC, Murthy KS, Naghavi M, Nahas Z, Naheed A, Naidoo KS, Naldi L, Nand D, Nangia V, Narayan KM, Nash D, Neal B, Nejjari C, Neupane SP, Newton CR, Ngalesoni FN, Ngirabega Jde D, Nguyen G, Nguyen NT, Nieuwenhuijsen MJ, Nisar MI, Nogueira JR, Nolla JM, Nolte S, Norheim OF, Norman RE, Norrving B, Nyakarahuka L, Oh IH, Ohkubo T, Olusanya BO, Omer SB, Opio JN, Orozco R, Pagcatipunan RS, Jr., Pain AW, Pandian JD, Panelo CI, Papachristou C, Park EK, Parry CD, Paternina

Caicedo AJ, Patten SB, Paul VK, Pavlin BI, Pearce N, Pedraza LS, Pedroza A, Pejin Stokic L, Pekericli A, Pereira DM, Perez-Padilla R, Perez-Ruiz F, Perico N, Perry SA, Pervaiz A, Pesudovs K, Peterson CB, Petzold M, Phillips MR, Phua HP, Plass D, Poenaru D, Polanczyk GV, Polinder S, Pond CD, Pope CA, Pope D, Popova S, Pourmalek F, Powles J, Prabhakaran D, Prasad NM, Qato DM, Quezada AD, Quistberg DA, Racape L, Rafay A, Rahimi K, Rahimi-Movaghar V, Rahman SU, Raju M, Rakovac I, Rana SM, Rao M, Razavi H, Reddy KS, Refaat AH, Rehm J, Remuzzi G, Ribeiro AL, Riccio PM, Richardson L, Riederer A, Robinson M, Roca A, Rodriguez A, Rojas-Rueda D, Romieu I, Ronfani L, Room R, Roy N, Ruhago GM, Rushton L, Sabin N, Sacco RL, Saha S, Sahathevan R, Sahraian MA, Salomon JA, Salvo D, Sampson UK, Sanabria JR, Sanchez LM, Sanchez-Pimienta TG, Sanchez-Riera L, Sandar L, Santos IS, Sapkota A, Satpathy M, Saunders JE, Sawhney M, Saylan MI, Scarborough P, Schmidt JC, Schneider IJ, Schottker B, Schwebel DC, Scott JG, Seedat S, Sepanlou SG, Serdar B, Servan-Mori EE, Shaddick G, Shahraz S, Levy TS, Shangguan S, She J, Sheikhbahaei S, Shibuya K, Shin HH, Shinohara Y, Shiri R, Shishani K, Shiue I, Sigfusdottir ID, Silberberg DH, Simard EP, Sindi S, Singh A, Singh GM, Singh JA, Skirbekk V, Sliwa K, Soljak M, Soneji S, Soreide K, Soshnikov S, Sposato LA, Sreeramareddy CT, Stapelberg NJ, Stathopoulou V, Steckling N, Stein DJ, Stein MB, Stephens N, Stockl H, Straif K, Stroumpoulis K, Sturua L, Sunguya BF, Swaminathan S, Swaroop M, Sykes BL, Tabb KM, Takahashi K, Talongwa RT, Tandon N, Tanne D, Tanner M, Tavakkoli M, Te Ao BJ, Teixeira CM, Tellez Rojo MM, Terkawi AS, Texcalac-Sangrador JL, Thackway SV, Thomson B, Thorne-Lyman AL, Thrift AG, Thurston GD, Tillmann T, Tobollik M, Tonelli M, Topouzis F, Towbin JA, Toyoshima H, Traebert J, Tran BX, Trasande L, Trillini M, Trujillo U, Dimbuene ZT, Tsilimbaris M, Tuzcu EM, Uchendu US, Ukwaja KN, Uzun SB, van de Vijver S, Van Dingenen R, van Gool CH, van Os J, Varakin YY, Vasankari TJ, Vasconcelos AM, Vavilala MS, Veerman LJ, Velasquez-Melendez G, Venketasubramanian N, Vijayakumar L, Villalpando S, Violante FS, Vlassov VV, Vollset SE, Wagner GR, Waller SG, Wallin MT, Wan X, Wang H, Wang J, Wang L, Wang W, Wang Y, Warouw TS, Watts CH, Weichenthal S, Weiderpass E, Weintraub RG, Werdecker A, Wessells KR, Westerman R, Whiteford HA, Wilkinson JD, Williams HC, Williams TN, Woldeyohannes SM, Wolfe CD, Wong JQ, Woolf AD, Wright JL, Wurtz B, Xu G, Yan LL, Yang G, Yano Y, Ye P, Yenesew M, Yentur GK, Yip P, Yonemoto N, Yoon SJ, Younis MZ, Younoussi Z, Yu C, Zaki ME, Zhao Y, Zheng Y, Zhou M, Zhu J, Zhu S, Zou X, Zunt JR, Lopez AD, Vos T, Murray CJ. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2287-323.

4. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2010;375(9710):181-3.

5. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122(3):248-56 e5.

6. Allman-Farinelli MA. Obesity and venous thrombosis: a review. Semin Thromb Hemost. 2011;37(8):903-7.

7. Stein PD, Matta F, Goldman J. Obesity and pulmonary embolism: the mounting evidence of risk and the mortality paradox. Thrombosis research. 2011;128(6):518-23.

8. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008;117(1):93-102.

9. Juhan-Vague I, Alessi MC, Mavri A, Morange PE. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. Journal of thrombosis and haemostasis : JTH. 2003;1(7):1575-9.

10. Escalante-Tattersfield T, Tucker O, Fajnwaks P, Szomstein S, Rosenthal RJ. Incidence of deep vein thrombosis in morbidly obese patients undergoing laparoscopic Roux-en-Y gastric bypass. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2008;4(2):126-30.
11. Arnold DM, Kahn SR, Shrier I. Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. Chest. 2001;120(6):1964-71.
12. Winegar DA, Sherif B, Pate V, DeMaria EJ. Venous thromboembolism after bariatric surgery performed by Bariatric Surgery Center of Excellence Participants: analysis of the Bariatric Outcomes Longitudinal Database. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2011;7(2):181-8.
13. Jamal MH, Corcelles R, Shimizu H, Kroh M, Safdie FM, Rosenthal R, Brethauer SA, Schauer PR. Thromboembolic events in bariatric surgery: a large multi-institutional referral center experience. Surgical endoscopy. 2015;29(2):376-80.
14. American Society for M, Bariatric Surgery Clinical Issues C. ASMBS updated position statement on prophylactic measures to reduce the risk of venous thromboembolism in bariatric surgery patients. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2013;9(4):493-7.
15. Finks JF, English WJ, Carlin AM, Krause KR, Share DA, Banerjee M, Birkmeyer JD, Birkmeyer NJ, Michigan Bariatric Surgery C, Center for Healthcare O, Policy. Predicting risk for venous thromboembolism with bariatric surgery: results from the Michigan Bariatric Surgery Collaborative. Annals of surgery. 2012;255(6):1100-4.
16. Bayer Pharma AG. Xarelto® (rivaroxaban) summary of product characteristics. . http://wwwemaeuropaeu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108pdf. 2013.
17. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther. 2005;78(4):412-21.
18. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373(9676):1673-80.
19. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. The New England journal of medicine. 2008;358(26):2765-75.
20. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. The New England journal of medicine. 2008;358(26):2776-86.
21. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372(9632):31-9.
22. Friedman RJ, Hess S, Berkowitz SD, Homering M. Complication rates after hip or knee arthroplasty in morbidly obese patients. Clinical orthopaedics and related research. 2013;471(10):3358-66.
23. Mueck W, Eriksson BI, Bauer KA, Borris L, Dahl OE, Fisher WD, Gent M, Haas S, Huisman MV, Kakkar AK, Kalebo P, Kwong LM, Misselwitz F, Turpie AG. Population pharmacokinetics and

pharmacodynamics of rivaroxaban--an oral, direct factor Xa inhibitor--in patients undergoing major orthopaedic surgery. Clin Pharmacokinet. 2008;47(3):203-16.
24. Duffull SB. Is the ideal anticoagulant a myth? Expert Rev Clin Pharmacol. 2012;5(3):231-6.
25. Asmis LM, Alberio L, Angelillo-Scherrer A, Korte W, Mendez A, Reber G, Seifert B, Stricker H, Tsakiris DA, Wuillemin WA. Rivaroxaban: Quantification by anti-FXa assay and influence on coagulation tests: a study in 9 Swiss laboratories. Thrombosis research. 2012;129(4):492-8.
26. Zurcher M, Sulzer I, Barizzi G, Lammle B, Alberio L. Stability of coagulation assays performed in plasma from citrated whole blood transported at ambient temperature. Thrombosis and haemostasis. 2008;99(2):416-26.
27. Chilver-Stainer L, Lammle B, Alberio L. Titre of anti-heparin/PF4-antibodies and extent of in vivo activation of the coagulation and fibrinolytic systems. Thrombosis and haemostasis. 2004;91(2):276-82.
28. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014;53(1):1-16.
29. Mueck W, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Kalebo P, Muelhofer E, Misselwitz F, Eriksson BI. Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thrombosis and haemostasis. 2008;100(3):453-61.
30. Chandler WL, Velan T. Estimating the rate of thrombin and fibrin generation in vivo during cardiopulmonary bypass. Blood. 2003;101(11):4355-62.
31. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. Journal of clinical pharmacology. 2007;47(2):218-26.

FIGURE LEGENDS

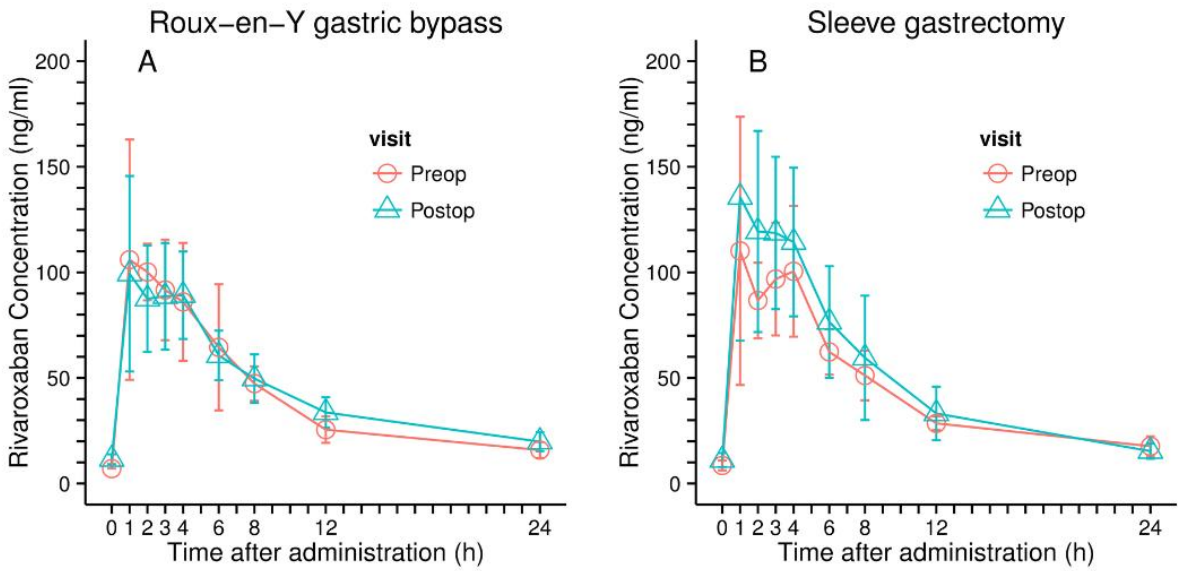

Figure 1 Rivaroxaban concentration: raw data by type of surgery; left Roux-en-Y Gastric bypass, right Sleeve gastrectomy

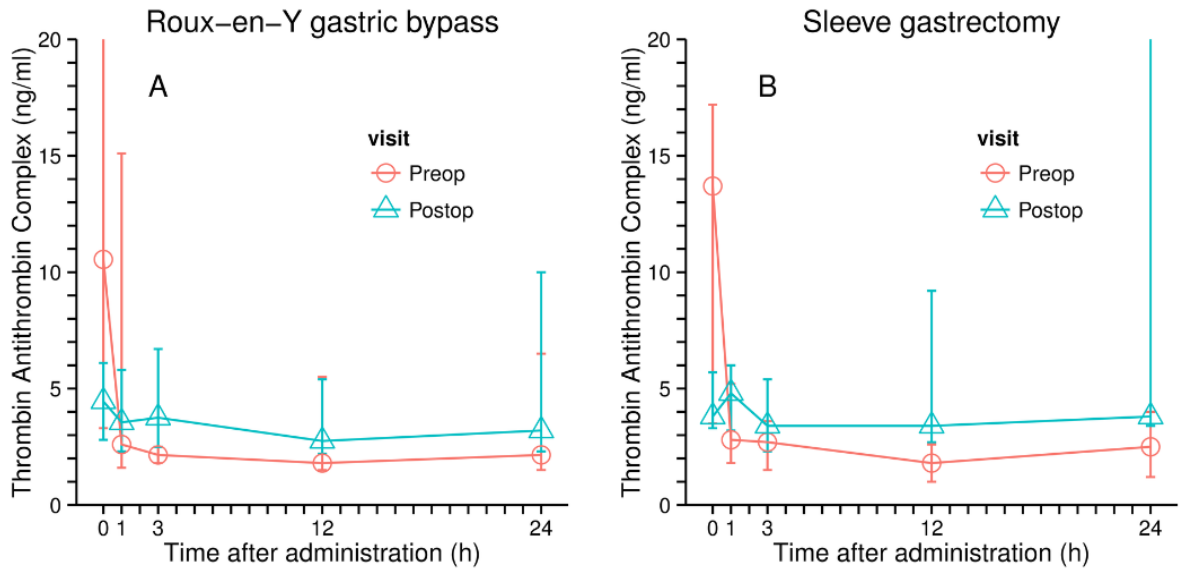

Figure 2 Thrombin-Antithrombin-Complexes (TAT) concentrations (median and range, n=6 RYGB, n=5 SG); left Roux-en-Y Gastric bypass, right Sleeve gastrectomy

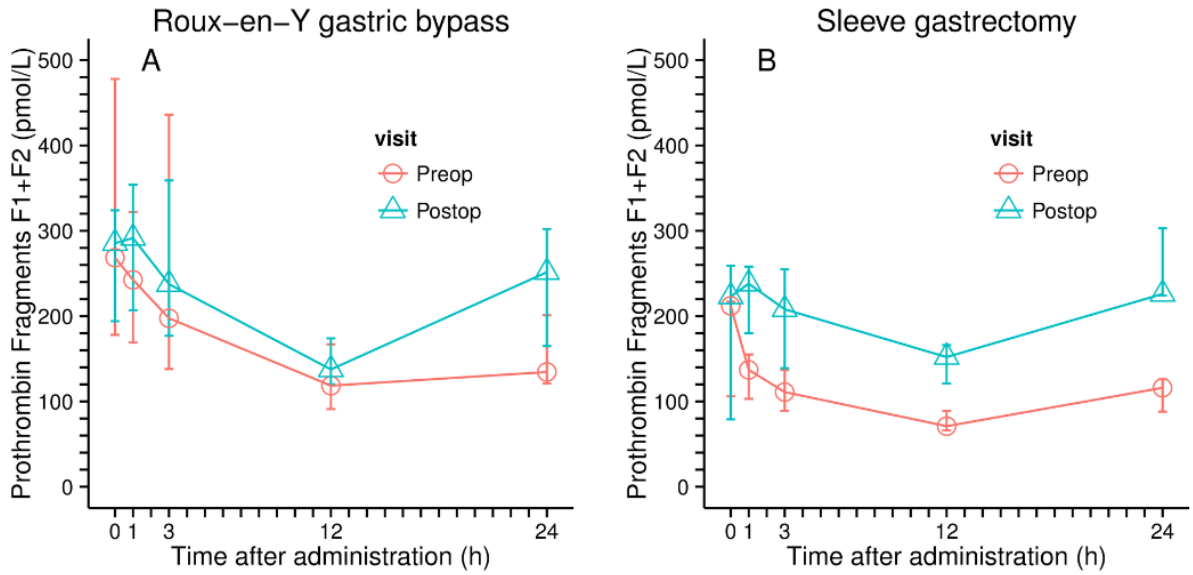

Figure 3 Prothrombin activation fragments F1+2 concentrations (median and range, n=6 RYGB, n=5 SG); left Roux-en-Y Gastric bypass, right Sleeve gastrectomy

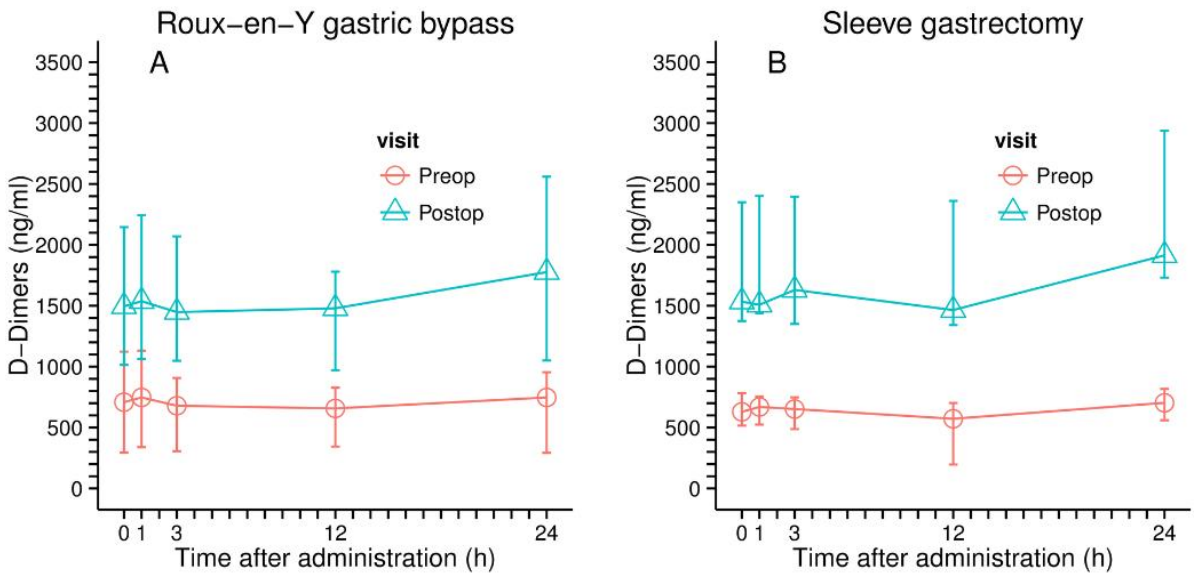

Figure 4 D-Dimers concentrations (median and range, n=6 RYGB, n=5 SG); left Roux-en-Y Gastric bypass, right Sleeve gastrectomy

Table 1

	Sleeve gastrectomy	Roux-en-Y Gastric bypass
n	6	6
Age, median (range)	37.7 (24-51)	39.0 (28-51)
Gender = male (%)	3 (50.0)	1 (16.7)
Weight median (range)	137.0 (112-153)	101.5 (96-120)
Height, median (range)	172.5 (167-190)	167.5 (156-171)
Body mass index, median (range)	44.6 (38.3-50.6)	38.2 (35.4-42.5)
ASA (%)		
2	1 (16.7)	2 (33.3)
3	3 (50)	4 (66.7)
4	2 (33.3)	0 (0.0)
eGFR (%)		
71	1 (16.7)	0 (0.0)
80	1 (16.7)	1 (16.7)
>90	4 (66.7)	5 (83.3)
Ethnicity = Caucasian (%)	6 (100.0)	6 (100.0)

Table 1: Baseline characteristics in the per protocol set; ASA: American Society of Anesthesiologists physical status classification system; eGFR: estimated glomerular filtration rate

Table 2

Patients	Parameters	Before surgery	After surgery	Ratio before surgery/ after surgery
All patients pooled	AUC (µg · h/L)	952.6 / 16.8	1095.5 / 16.8	0.87 [0.77;0.98]
	C_{max} (µg/L)	135.9 / 19.3	137.3 / 19.3	0.99 [0.79;1.24]
	$t_{1/2}$ (h)	13.5 / 38.8	11.6 / 38.8	1.16 [0.82;1.64]
	V_Z/f (L/kg)	47.9 / 22.3	44.4 / 22.3	1.08 [0.99;1.18]
	T_{max} (h)	1.5 (0.9-4)	2 (1-4)	NA
Roux-en-Y Gastric bypass	AUC (µg · h/L)	933.7 / 22.3	1029.4 / 22.3	0.91 [0.75;1.09]
	C_{max} (µg/L)	136.5 / 10.7	110.8 / 10.7	1.23 [0.91;1.66]
	$t_{1/2}$ (h)	13.8 / 46.6	15 / 46.6	0.92 [0.57;1.48]
	V_Z/f (L/kg)	55.3 / 22.5	52.7 / 22.5	1.05 [0.91;1.21]
	t_{max} (h)	1.5 (0.9-4)	2.5 (1-4)	NA
Sleeve gastrectomy	AUC (µg · h/L)	971.9 / 10.6	1165.8 / 10.6	0.83 [0.68;1.02]
	C_{max} (µg/L)	135.3 / 26.7	170.0 / 26.7	0.8 [0.59;1.08]
	$t_{1/2}$ (h)	13.1 / 34.1	8.9 / 34.1	1.47 [0.82;2.64]
	V_Z/f (L/kg)	41.5 / 9.5	37.4 / 9.5	1.11 [0.95;1.29]
	t_{max} (h)	1.5 (1-4)	1.5 (1-4)	NA

Table 2: Pharmacokinetic parameters for all patients (summarized), and Roux-en-Y gastric bypass as well as Sleeve gastrectomy patients (separated); before and after surgery the geometric mean and the coefficient of variation is presented. For t_{max} the median and the range is presented. The ratio before surgery/after surgery is presented together with its 95% confidence interval.

AUC area under the plasma-concentration time curve from time 0 to infinity, C_{max} peak plasma concentration, $t_{1/2}$ terminal half-life, $V_{z/f}$ (Dose/C_0)/bodyweight apparent volume of distribution during the terminal phase divided by total body weight (in kg), t_{max} time to peak plasma concentration

Table 3

ID	Diagnosis	Symptoms	AE grade	SAE	Relationship to study drug	Change of study intervention
1	Head ache	Headache	mild	no	unlikely	no change
2	Granuloma liver		mild	no	unlikely	no change
3	Headache	Headache	mild	no	unlikely	no change
3	Koprostase	Abdominal pain	mild	no	unlikely	no change
5	Nausea	Nausea	mild	no	unlikely	no change
6	Jejuneal obstruction	Abdominal pain	severe	yes	unlikely	withdrawn
6	Superficial surgical site infection		moderate	no	unlikely	no change
6	Deep surgical site infection		moderate	no	unlikely	no change
7	Headache	Headache	mild	no	unlikely	no change
8	Headache	Headache	mild	no	unlikely	no change
9	Nausea		moderate	no	unlikely	no change
9	Dizziness		moderate	no	unlikely	no change
9	Hematoma of abdominal wall near incision		mild	no	possible	no change
9	Low Hemoglobin (72 g/L)		moderate	no	possible	no change
9	Impaired oesophagogastral transit of gastrographin	Vomiting	mild	no	unlikely	no change

ID	Hospitalization prolonged	Drug therapy		Other action taken		Death	Life threatening
1	no	no		no			
2	no	no		no			
3	no	no		no			
3	no	yes	metamizole	no			
5	no	yes	metoclopramide	no			
6	yes	no		yes	reintervention	no	yes
6	no	no		yes	vacuum therapy of laparatomy wound drainage		
6	no	no		yes			
7	no	yes	paracetamol	no			
8	no	yes	paracetamol	no			
9	no	yes	metoclopramide	no			
9	no	no		no			
9	no	no		no			
9	no	yes	ferrinject (ferric carboxymaltose)	no			
9	no	no		no			

Table 3: Adverse events and safety measures taken; AE adverse event, SAE serious adverse event